



Pfizer and Ionis Announce Discontinuation of Vupanorsen Clinical Development Program

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NEW YORK and CARLSBAD, Calif., January 31, 2022 — Pfizer Inc. (NYSE: PFE) and Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced the discontinuation of the Pfizer-led clinical development program for vupanorsen (PF-07285557), an investigational antisense therapy that was being evaluated for potential indications in cardiovascular (CV) risk reduction and severe hypertriglyceridemia (SHTG).

Pfizer made this decision after a thorough review of data from the global Phase 2b, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, 8-arm parallel-group study of vupanorsen in statin-treated participants with dyslipidemia — also known as **TaR**geting **ANG**PTL3 with an **aNtiSense oLigonucleotide** in **AdulTs** with dyslipid**Emia** (TRANSLATE-TIMI 70). As previously announced, the study met its primary endpoint, achieving a statistically significant reduction in non-high density lipoprotein cholesterol (non-HDL-C) — as well as statistically significant reductions in triglycerides (TG) and angiopoietin-like 3 (ANGPTL3). However, the magnitude of non-HDL-C and TG reduction observed did not support continuation of the clinical development program for CV risk reduction or SHTG. Vupanorsen was also associated with dose-dependent increases in liver fat, and higher doses were associated with elevations in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Pfizer will return development rights to vupanorsen to Ionis, from which it licensed the investigational therapy in a worldwide exclusive agreement in November 2019.

“While this outcome is disappointing, the clinical and scientific knowledge derived from the vupanorsen program will hopefully contribute to a greater understanding of cardiovascular risk reduction and severe hypertriglyceridemia and the current gaps in treating these conditions,” said James Rusnak, M.D., Ph.D., Senior Vice President and

Chief Development Officer, Internal Medicine and Hospital, Pfizer. “Pfizer remains dedicated to research and development in the cardiovascular category and helping to address the unmet medical needs of patients with cardiovascular diseases. We are grateful to the patients, investigators and support staff who have participated in this important research program.”

“Although this is not the outcome we would have liked, we are grateful for this collaboration with Pfizer, whose leadership in the development of vupanorsen has been instrumental in gaining important insights and learnings that will help us continue to deliver potentially life-transforming treatments for people impacted by cardiovascular disease,” said Richard S. Geary, Ph.D., Executive Vice President and Chief Development Officer at Ionis.

About Vupanorsen Vupanorsen is an investigational antisense therapy discovered by Ionis. Vupanorsen acts through a novel mechanism, targeting ANGPTL3, a genetically validated target of lipoprotein metabolism.¹ Vupanorsen uses Ionis’ advanced Ligand Conjugated Antisense (LICA) technology platform. The potential therapeutic benefits of ANGPTL3 reduction are supported by the discovery that people with a genetic deficiency in ANGPTL3 have reduced levels of LDL-C and TG, and a decreased risk of coronary artery disease.²

References ¹Endocrine. 2016 Jan 11;52(2):187-193. ²JAMA Cardiol. 2018 Oct 1;3(10):957-966.

About Pfizer: Breakthroughs That Change Patients’ Lives At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world’s premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 170 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at @Pfizer and @PfizerNews, LinkedIn, YouTube and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer).

Pfizer Disclosure Notice The information contained in this release is as of January 31, 2022. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer's research and development in the cardiovascular category, including its potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when drug applications may be filed in any jurisdictions for any potential product candidates; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether any such product candidates will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of any such product candidates; the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2020 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

About Ionis Pharmaceuticals, Inc. For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing the standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry leading neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies. To learn more about Ionis visit

www.ionispharma.com or follow us on Twitter @ionispharma.

Ionis' Forward-looking Statement This press release includes forward-looking statements regarding Ionis' business, and the therapeutic and commercial potential of vupanorsen and Ionis' technologies and products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2020, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available from the Company.

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